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Debra D. Pittman

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EMCH, GREGORY S

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/643,589	Applicant(s) PITTMAN ET AL.	
	Examiner Gregory S. Emch	Art Unit 1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 July 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,8,12-58 and 85-87 is/are pending in the application.
- 4a) Of the above claim(s) 32-41,45-58 and 85-87 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,8,12-31 and 42-44 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>11/18/09</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Response to Amendment

Claims 1, 16 and 43 have been amended, and claims 9-11 have been canceled as requested in the amendment filed on 06 February 2009. Following the amendment, claims 1, 8, 12-58 and 85-87 are pending in the instant application.

Claims 32-41, 45-58 and 85-87 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the replies filed on 24 August 2006 and 23 July 2007.

Claims 1, 8, 12-31 and 42-44 are under examination in the instant office action.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 18 November 2009 was filed after the mailing date of the non-final rejection on 18 March 2009. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Withdrawn Rejections

The rejection of claims 9-11 under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,864,018 to Morser et al., and as evidenced by Neeper et al. (J Biol Chem. 1992) is withdrawn as moot in response to the cancellation of said claims.

Remaining issues are set forth below.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 8 and 19 stand rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,864,018 to Morser et al. (issued 26 January 1999; filed 16 April 1996; citation AA on IDS dated 01 March 2004), as evidenced by Neeper et al. (J Biol Chem. 1992; Citation U on PTO-892 dated 18 March 2009) and as newly evidenced by Mjalli et al. (US 20060078562A1, published 13 April 2006, earliest priority date of 03 August 2004).

The Morser patent teaches that polypeptides of the invention include RAGE polypeptides and those that are related to and/or derived from human RAGE polypeptides (col.5, lines 3-6). Although the patent does not explicitly recite the sequence information for full-length human RAGE, it inherently teaches such, since it teaches the term "RAGE polypeptide" (see e.g. col.2, lines 45-47; col.8, lines 7-14). Accordingly, this human RAGE polypeptide comprises amino acid residues 1-404 of SEQ ID NO: 7, and this sequence information was well known in the art at the time of filing, as evidenced by Neeper et al. (see p.15001, Figure 3). Thus, the Morser patent inherently teaches a RAGE polypeptide, which is 100% identical to the instant SEQ ID NO: 7. The instant specification at p.10, lines 29-32, line states, "The terms "fusion

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protein" and "chimeric protein" are interchangeable and refer to a protein or polypeptide that has an amino acid sequence having portions corresponding to amino acid sequences from two or more proteins. The sequences from two or more proteins may be full or partial (i.e., fragments) of the proteins." The instant specification at p.17, lines 10-19 states that an immunoglobulin element may be any portion of an immunoglobulin. Thus, this limitation encompasses any portion of any immunoglobulin domain of any antibody. Accordingly, Morser's disclosure of full-length human RAGE, i.e. residues 1-404 of SEQ ID NO: 7 meets the disclosure's definition of a fusion protein and meets the limitations of the claims because it is a polypeptide that has an amino acid sequence having portions corresponding to amino acid sequences from two or more proteins, i.e. a RAGE-LBE and a portion of an immunoglobulin. That is, it comprises a RAGE-LBE, wherein the RAGE-LBE consists of amino acid residues 1-344 of SEQ ID NO: 7 and it comprises e.g. Pro-Glu-Asn at residues 376-378. The three amino acid sequence of Pro-Glu-Asn meets the limitation of an "immunoglobulin element" because it is a portion of an immunoglobulin domain of an antibody, as evidenced by Mjalli et al. (see Mjalli's paragraph [0018] and SEQ ID NO: 38, which is a partial amino acid sequence for the C_H2 and C_H3 domains of human IgG and which comprises Pro-Glu-Asn). Therefore, Morser's disclosure of full-length human RAGE anticipates independent claim 1 because it comprises a RAGE-LBE, wherein the RAGE-LBE consists of amino acid residues 1-344 of SEQ ID NO: 7 and it comprises an immunoglobulin element i.e. Pro-Glu-Asn at residues 376-378. The intervening amino acid residues (i.e., residues 345-

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375) can be considered to be a linker, which is taught to be with the scope of the claims (see the instant specification at p.11, lines 1-2).

Moreover, as stated previously, the instant specification teaches that a peptide comprising residues 1-329 of RAGE also comprises Ig1, Ig2 and Ig3 domains (see Figure 5). Thus, since the patent teaches human RAGE, the patent inherently teaches that the RAGE-LBE comprises Ig1, Ig2, and Ig3 domains (as evidenced by applicant's Figure 5 which shows the location of these Ig domains). Applicants are reminded that chemical compounds and their properties are inseparable (*In re Papesch*, 315 F.2d 381,137 USPQ 43 (CCPA1963)), as are their processes and yields (*In re Von Schickh*, 362 F.2d 821,150 USPQ 300 (CCPA 1966)). Therefore, the Morser patent teaches the limitations of claim 8. The patent teaches pharmaceutical compositions comprising the polypeptides of the invention and a pharmaceutically acceptable carrier (co1.19, lines 21-24; col.20, lines 12-20), thus meeting the limitations of claim 19.

In the reply filed on 09 July 2009, applicants assert that Morser et al. only disclose a fragment of human RAGE having 340 amino acids in length and that Morser et al. do not teach the full-length human RAGE. Applicants assert that even assuming Morser inherently disclosed the full-length human RAGE, applicants disagree with the examiner's claim construction. Applicants assert that the claims must be interpreted in light of the teachings of the specification. Applicants assert that the specification defines the term "RAGE-LBE" on page 12, lines 10-13 as "any extracellular portion of a transmembrane RAGE polypeptide (e.g., soluble RAGE) and fragments thereof that

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retain the ability to bind a RAGE ligand". Applicants assert that as such, one of skill in the art would not construe the term "RAGE-LBE" to include the full-length human RAGE. Applicants assert that the claims are directed to "a **fusion protein** comprising a RAGE-LBE and an immunoglobulin element, rather than the wild-type human RAGE protein alone" (Emphasis in original). Applicants further assert that in light of the description of the term "immunoglobulin element" in the specification (e.g., page 17, lines 10-19), one of skill in the art would know that the term "immunoglobulin element" refers to a heterologous sequence, not including the Ig1, Ig2, and Ig3 domains which are inherently present in the wild-type human RAGE sequence. Applicants assert that Morser et al. do not teach a RAGE-LBE which consists of amino acid residues 1 through 344 of SEQ ID NO: 7, as recited in independent claims 1, 20, and 43.

Applicants' arguments have been fully considered and are not found persuasive. As set forth above, the Morser patent teaches that polypeptides of the invention include RAGE polypeptides and those that are related to and/or derived from human RAGE polypeptides (col.5, lines 3-6). Although the patent does not explicitly recite the sequence information for full-length human RAGE, it inherently teaches such, since it teaches the term "RAGE polypeptide" (see e.g. col.2, lines 45-47; col.8, lines 7-14). Accordingly, this human RAGE polypeptide comprises amino acid residues 1-404 of SEQ ID NO: 7, and this sequence information was well known in the art at the time of filing, as evidenced by Neeper et al. (see p.15001, Figure 3). Thus, contrary to applicants' assertion, the Morser patent inherently teaches full-length human RAGE, which is 100% identical to the instant SEQ ID NO: 7.

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Moreover, the examiner agrees that claims are given broadest reasonable interpretation, which is construed in light of the teachings of the specification. As set forth above, the instant specification at p.10, lines 29-32 states, "The terms "fusion protein" and "chimeric protein" are interchangeable and refer to a protein or polypeptide that has an amino acid sequence having portions corresponding to amino acid sequences from two or more proteins. The sequences from two or more proteins may be full or partial (i.e., fragments) of the proteins." The instant specification at p.17, lines 10-19 states that an immunoglobulin element may be any portion of an immunoglobulin. Thus, this limitation encompasses any portion of any immunoglobulin domain of any antibody. Accordingly, Morser's disclosure of full-length RAGE, i.e. residues 1-404 of SEQ ID NO: 7 meets the disclosure's definition of a fusion protein and meets the limitations of the claims because it is a polypeptide that has an amino acid sequence having portions corresponding to amino acid sequences from two or more proteins, i.e. a RAGE-LBE and a portion of an immunoglobulin. That is, it comprises a RAGE-LBE, wherein the RAGE-LBE consists of amino acid residues 1-344 of SEQ ID NO: 7 and it comprises e.g. Pro-Glu-Asn at residues 376-378. The three amino acid sequence of Pro-Glu-Asn meets the limitation of an immunoglobulin element because it is a portion of an immunoglobulin domain of an antibody, as evidenced by Mjalli et al. (see Mjalli's paragraph [0018] and SEQ ID NO: 38, which is a partial amino acid sequence for the C_H2 and C_H3 domains of human IgG and which comprises Pro-Glu-Asn). Therefore, Morser's disclosure of full-length human RAGE anticipates independent claim 1 because it comprises a RAGE-LBE, wherein the RAGE-LBE consists of amino acid

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residues 1-344 of SEQ ID NO: 7 and it comprises an immunoglobulin element i.e. Pro-Glu-Asn at residues 376-378. The intervening amino acid residues (i.e., residues 345-375) can be considered to be a linker, which is taught to be with the scope of the claims (see the instant specification at p.11, lines 1-2).

Regarding applicants' assertion that one of skill in the art would not construe the term "RAGE-LBE" to include the full-length human RAGE, the RAGE-LBE is not considered to include full-length RAGE. Rather, full-length RAGE meets the limitations of the entire claimed "fusion protein." It is noted that "fusion protein" describes how the protein is made and does not describe the protein's structure. That is, it is a "product-by-process" limitation referring to the process of linking nucleic acids encoding different amino acids. Thus, the patentability of the product is based on the product itself and does not depend on its method of isolation (see MPEP §2113). Since the prior art reference by Morser teaches the product, i.e. it describes the structural limitations of the claims, it anticipates the claimed invention, even though it is made by a different process. That is, full-length RAGE meets the structural requirements set forth in the body of independent claim 1, and thus, the claims are anticipated. Applicants bear the burden of establishing a patentable distinction between the claimed fusion protein and the prior art protein of Morser. It is suggested that applicants amend independent claim 1 to better define the claimed "immunoglobulin element" such that the fusion protein is distinguished from proteins in the prior art. For example, if applicants incorporated the limitations of some the dependent claims (e.g. "wherein said immunoglobulin element comprises an immunoglobulin heavy chain" as recited by claim 12, "wherein said

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immunoglobulin element comprises an Fc domain” as recited by claim 13 or “wherein said immunoglobulin element comprises CH1 and Fc domains” as recited by claim 16) into independent claim 1, such would overcome the instant rejection under 35 U.S.C. 102(b). Such an amendment would also simplify the issues for appeal.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicants are advised of the

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obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 8, 13 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,864,018 to Morser et al. (issued 26 January 1999; filed 16 April 1996; citation AA on IDS dated 01 March 2004), in view of Neeper et al. (J Biol Chem. 1992; Citation U on PTO-892 dated 18 March 2009), and further in view of Peppel et al. (J Exp Med 1991; citation U on PTO-892 dated 18 October 2007).

It is noted that this is a new rejection necessitated by the amendment to independent claim 1, i.e. that the RAGE-LBE consists of amino acids 1-344 of SEQ ID NO: 7.

Morser teaches RAGE polypeptides including RAGE, fragments and derivatives of full length RAGE, e.g. soluble RAGE (sRAGE) and fusion proteins comprising any of these RAGE polypeptides (see col.5, lines 3-32; col.8, lines 7-29). Examples of RAGE polypeptides include Morser's SEQ ID NO: 2 (residues 1-340 of RAGE) and Morser's SEQ ID NO: 4 (residues 23-340 of RAGE, see columns 29-34). The difference between the disclosure of the Morser et al. patent and the claimed invention is that the patent does not teach a fusion protein comprising a RAGE-LBE consisting of residue 1-344 of SEQ ID NO: 7 and an immunoglobulin element that is not inherent to the structure of RAGE, e.g. a portion of a separate antibody fused to the RAGE-LBE.

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However, Neeper et al. teach that the extracellular (i.e. soluble) domain of human RAGE is amino acids 1-344 of RAGE (see Figure 4, p.15002). Neeper et al. teach that there are likely several types of AGE-binding proteins (of which soluble RAGE polypeptides are examples) potentially recognizing different AGE ligands or activating distinct cellular processes following formation of the ligand/receptor complex (see p.15003, 3rd full paragraph). Neeper et al. do not teach a fusion protein comprising residues 1-344 of SEQ ID NO: 7 and an immunoglobulin element, e.g. a portion of a separate antibody fused to the RAGE-LBE.

However, Peppel et al. teach fusion proteins comprising a soluble extracellular receptor moiety of TNF- α linked to an immunoglobulin element, wherein the immunoglobulin element comprises the C_H2 and C_H3 domain of human IgG1, i.e. the Fc domain (p.1483, paragraph 3 – p.1484, paragraph 4), as in claim 13. The Peppel reference teaches that the fusion protein is an effective inhibitor of the ligand-receptor interaction (entire document, e.g. abstract). Furthermore, the Peppel et al. reference teaches that truncated receptor molecules, i.e. fragments that lack the transmembrane or cytoplasmic domains, are capable of interacting with TNF and can act as antagonists of TNF and as reagents to be used in defining the interaction between TNF and its receptor (ligand/receptor). The Peppel et al. reference teaches the desirability (e.g. increased stability and ease of purification) of engineering a chimeric protein in which the extracellular domain of the receptor, which normally engages the ligand, is covalently linked to IgG immunoglobulin domains (p.1483). Peppel et al. do not teach a fusion protein comprising residues 1-344 of SEQ ID NO: 7.

As evidenced by the Morser et al. patent, the artisan of ordinary skill would have known that the interaction between AGE and RAGE is implicated in numerous pathological disease states and that improved inhibitors of this interaction, e.g. soluble RAGE polypeptides would be desirable (see col.5, lines 3-32; col.8, lines 7-29). As evidenced by the Neeper et al. reference, the artisan of ordinary skill would have known that soluble RAGE is residues 1-344 of SEQ ID NO: 7 and that AGE ligands bind to multiple proteins (see Figure 4, p.15002; p.15003, 3rd full paragraph). As evidenced by the Peppel et al. reference, the artisan of ordinary skill would have recognized the desirability creating a construct, which comprises a soluble extracellular receptor moiety linked to an Fc domain of an immunoglobulin for inhibiting a ligand-receptor interaction (p.1483, paragraph 3 – p.1484, paragraph 4).

Given that Morser et al. teach that RAGE-LBE fusion proteins, including soluble RAGE fusion proteins, are useful inhibitors of AGE/RAGE interaction, given that Neeper et al. teach that soluble RAGE is residues 1-344 of human RAGE and given that Peppel et al. teach that an extracellular receptor moiety-Fc fusion protein is an effective inhibitor for the ligand-receptor interaction, it would have been reasonable to predict that a fully functional fusion protein comprising the RAGE polypeptide disclosed by Morser et al. and Neeper et al. and comprising the Fc fragment taught by Peppel et al. could be successfully produced and used for treatment of inflammatory disease. This is because Morser's disclosure concerning RAGE is analogous to Peppel's disclosure concerning TNF. See for example, col.1, lines 40-64 of Morser, which teaches that the AGE/RAGE interaction is implicated in the inflammatory response, where it leads to activation of

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TNF inflammatory cascades. Morser teaches that a soluble RAGE polypeptide is useful as an inhibitor of the ligand/receptor interaction (i.e. AGE/RAGE interaction) which is implicated in inflammatory disease. Similarly, Peppel teaches that a soluble TNF receptor is useful as an inhibitor of the ligand/receptor interaction (i.e. TNF/TNF receptor interaction) that is implicated in the same inflammatory pathway as RAGE in inflammatory disease. Therefore, both references teach using extracellular portions of the receptors as potential blocking agents of the ligand/receptor interaction for the same inflammatory pathway. Accordingly, one of ordinary skill in the art would have found it obvious to attempt to generate a RAGE fusion protein linked to an IgG immunoglobulin domain because Peppel teaches the desirability (e.g. increased stability and ease of purification) of engineering a chimeric protein in which the extracellular domain of the receptor, which normally engages the ligand, is covalently linked to IgG immunoglobulin domains (p.1483). Moreover, Morser's explicit example of a soluble RAGE polypeptide (i.e. comprising 1-340 of SEQ ID NO: 7) only differs by 4 amino acids from that of Neeper. The artisan of ordinary skill would have been motivated to substitute residues 1-344 of RAGE in place of residues 1-340 because Morser discloses using the soluble portion of RAGE in general (col.5, lines 3-32; col.8, lines 7-29) and Neeper demonstrated that residues 1-344 make up the soluble portion of RAGE (Figure 4). Thus, it would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to improve Morser's soluble RAGE fusion protein as disclosed by Neeper and Peppel to yield predictable results. This is because the artisan

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has good reason to pursue the known options within his or her technical grasp (see *KSR International Co. v. Teleflex Inc. (KSR)*, 550 U.S. ____, 82 USPQ2d 1385 (2007)).

In the reply filed on 09 July 2009, applicants assert that Morser et al. fail to teach or suggest a RAGE-LBE which consists of amino acid residues 1 through 344 of SEQ ID NO: 7, as recited in claims 1, 20 or 43. Applicants assert that the other cited references (Neeper et al. and Peppel et al.) fail to overcome the deficiencies of Morser et al. Applicants assert that even if the Morser reference is to be combined with the other cited references, the combination fails to provide any motivation or reasonable expectation of success for a artisan of ordinary skill to modify Morser's RAGE polypeptides to arrive at the claimed RAGE-LBE fusion proteins. Applicants assert that Morser et al. provide no teaching or suggestion to modify RAGE polypeptides to improve their suitability or efficacy for any application. Applicants assert that there is simply no common connection between the cited disclosures that would have motivated an artisan of ordinary skill to combine these teachings to make RAGE- LBE fusion proteins such as those claimed in the present application. Applicants assert that Morser et al. fail to guide one of skill in the art to successfully select and make the RAGE-LBE fusion protein as claimed.

Applicants' arguments have been fully considered and are not found persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871

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(CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Neeper et al. teaches the claimed RAGE-LBE of residues 1-344 of SEQ ID NO: 7 and that there are likely several types of AGE-binding proteins (of which soluble RAGE polypeptides are examples) potentially recognizing different AGE ligands or activating distinct cellular processes following formation of the ligand/receptor complex (see p.15003, 3rd full paragraph). Given these teachings, the artisan of ordinary skill would have at least been motivated to try to use a polypeptide consisting of residues 1-344 of SEQ ID NO: 7 to optimize the general disclosure of RAGE fusion proteins disclosed by Morser. It is noted that Morser's explicit example of a soluble RAGE polypeptide (i.e. comprising 1-340 of SEQ ID NO: 7) only differs by 4 amino acids from that of Neeper. The artisan of ordinary skill would have been motivated to substitute residues 1-344 of RAGE in place of residues 1-340 because Morser discloses using the soluble portion of RAGE in general (col.5, lines 3-32; col.8, lines 7-29) and Neeper demonstrated that residues 1-344 make up the soluble portion of RAGE (Figure 4).

Regarding applicants' assertion that Morser provides no teaching or suggestion that RAGE polypeptides need to be further modified, the fusion proteins are taught as potentially useful in providing for enhanced expression of the RAGE polypeptide constructs, or in producing RAGE polypeptides having other desirable properties, e.g., labeling groups, e.g., enzymatic reporter groups, binding groups, antibody epitopes, etc. This general disclosure of potential uses for the fusion proteins of Morser et al. would motivate the artisan to search the art for more specific polypeptides for inclusion with said fusion proteins. Additionally, applicants' assertion that there is no common

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connection between the cited disclosures that would have motivated the artisan of ordinary skill to combine these teachings is inaccurate. As set forth above, Morser teaches that the AGE/RAGE interaction is implicated in the inflammatory response, where it leads to activation of TNF inflammatory cascades (col.1, lines 40-64). This suggests that blocking either TNF signaling or AGE/RAGE signaling would be useful to treat inflammation. Moreover, Morser teaches that a soluble RAGE polypeptide is useful as an inhibitor of the ligand/receptor interaction (i.e. AGE/RAGE interaction) that is implicated in inflammatory disease. Similarly, Peppel teaches that a soluble TNF receptor is useful as an inhibitor of the ligand/receptor interaction (i.e. TNF/TNF receptor interaction) that is implicated in inflammatory disease. Therefore, both references teach using extracellular portions of the receptors as potential blocking agents of the ligand/receptor interaction that is implicated in inflammatory disease.

Accordingly, one of ordinary skill in the art would have found it obvious to attempt to generate a RAGE fusion protein linked to an IgG immunoglobulin domain because of the advantages of doing so as taught by Peppel. Peppel teaches the desirability (e.g. increased stability and ease of purification) of engineering a chimeric protein in which the extracellular domain of the receptor, which normally engages the ligand, is covalently linked to IgG immunoglobulin domains (p.1483). At the time of the invention, all of the reagents were readily available and the technology existed to prepare fusion proteins as claimed and Peppel had demonstrated success in producing fusion proteins useful for therapeutic purposes with no loss of function. It would have been customary for an artisan of ordinary skill to determine the optimal fusion protein partner for

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inclusion with the RAGE-LBE given Peppel's explicit teachings of how to design such. Thus, one skilled in the art could have readily modified the RAGE-LBE containing fusion proteins of Morser by optimizing them for therapeutic use as taught by Neeper and Peppel. Moreover, the motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose (MPEP §2144.07). Thus, contrary to applicants' assertions, it would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to improve Morser et al.'s soluble RAGE fusion protein as disclosed by Neeper et al. and Peppel et al. to yield predictable results. Based on the analogous disclosures of the prior art references of record, it would at least be obvious to try generate the claimed fusion protein, which is proper to support a finding of obviousness under 35 U.S.C. 103(a). See the Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1396) (available at <http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf>).

Claims 12, 14-18, 20-31 and 42-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,864,018 to Morser et al., in view of Neeper et al. and Peppel et al. as applied to claims 1, 8, 13 and 19 above, and further in view of U.S. 20020102604 to Milne Edwards et al. (citation A on PTO-892 dated 26 September 2006; published 01 August 2002, filed 07 December 2000) and as evidenced by WO

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94/10308 to Spriggs et al. (citation N on PTO-892 dated 26 September 2006; published 11 May 1994).

The Morser et al., Neeper et al. and Peppel et al. references teach as set forth above. The references fail to teach the remaining elements of the fusion proteins of claims 12, 14-18, 20-31 and 42-44.

However, U.S. 20020102604 to Milne Edwards et al. teaches fusion proteins comprising polypeptides of the invention and functional fragments thereof for the treatment of inflammatory disorders (e.g. paragraphs 0117, 0176, 0230 and 0708). The reference teaches antibodies and fragments thereof, (including heavy chains [VH], Fc domains and CH1 domains) as potential partners in the fusion proteins (paragraphs 0364, 0376 and 0377), as in claims 12 and 14-16. The '604 publication teaches that the fusions can comprise any combination of the above-mentioned antibody fragments or domains (0376 and 0377), as in claim 16. The '604 publication teaches dimerizing polypeptides, including leucine zippers, as part of the fusions proteins of the invention and teaches that these dimerizing polypeptides are useful to create soluble multimeric fusion proteins, which may offer the advantage of enhanced biological activity (0312-0315), as in claims 18, 20, 27 and 31. Also, at paragraph 0314, the '604 publication states "examples of leucine zipper domains suitable for producing soluble multimeric proteins of the invention are those described in PCT application WO 94/10308, hereby incorporated by reference." Accordingly, WO 94/10308 to Spriggs et al. teaches jun and fos leucine zippers (p.1, line 34 – p.2, line 2), as in claims 28 and 29. The '604 publication teaches stabilizing polypeptides (1260), targeting polypeptides (1679), and

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purification polypeptides (0176) as part of the fusion proteins of the invention, as in claim 20. The '604 publication also teaches that the dimerizing polypeptide can be amphiphilic polypeptides and fragments thereof as part of the fusion proteins (1679), as in claim 21, and teaches that fragments of polypeptides can be at least 6, at least 8 to 10, 12, 15, 20, 25, 30, 35, 40, 50, 60, 75, 100, 125, 150, 175, 200, 225, 250, 275, 300, 350, 400, 450 or 500 amino acids (0333), as in claims 22-25. The '604 publication teaches a peptide helix bundle (0671), as in claim 26, and teaches that formation of multimers (e.g. dimerization) can be the result of ionic interaction (i.e., oppositely charged polypeptides bound to each other; 0312), as in claim 30. The '604 document teaches protein complexes, comprising a protein of the invention (e.g. 0667), as in claim 42. The '604 document teaches TNF- α inhibitors (e.g., uromodulin) as part of pharmaceutical compositions of the invention (para. 0825), as in claims 43 and 44.

None of the cited references teach a fusion protein, wherein said immunoglobulin element comprises a CH1 domain of a first immunoglobulin class and a CH1 domain of a second immunoglobulin class, wherein the first and second immunoglobulin classes are not the same. However, in the instant case this is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize.

Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ (see MPEP § 2144.05). It would have been customary for an artisan of ordinary skill to determine the optimal immunoglobulin composition of the fusion protein of claim 17 by varying the immunoglobulin type in order to best achieve the desired results. Thus, absent some demonstration of unexpected results

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from the claimed parameters, this optimization of immunoglobulin type would have been obvious at the time of applicants' invention.

As evidenced by the Morser et al. patent, the artisan of ordinary skill would have known that the interaction between AGE and RAGE is implicated in numerous pathological disease states and that improved inhibitors of this interaction would be desirable. As evidenced by the Neeper et al. reference, the artisan of ordinary skill would have known that soluble RAGE is residues 1-344 of SEQ ID NO: 7 and that AGE ligands bind to multiple proteins (see Figure 4, p.15002; p.15003, 3rd full paragraph). As evidenced by the Peppel et al. reference, the artisan of ordinary skill would have recognized the desirability creating a construct, comprising a soluble extracellular receptor moiety linked to an Fc domain of an immunoglobulin for inhibiting a ligand-receptor interaction. As evidenced by Milne Edwards et al. in view of Spriggs et al., the artisan of ordinary skill would have been motivated to include the fusion protein partners disclosed therein with RAGE-LBEs because Milne Edwards et al. teaches that these would provide soluble multimeric fusion proteins with increased biological activity for treatment of inflammation (e.g. 0117, 0176, 0230, 0312-0315 and 0708). Given that Morser et al. teach that RAGE-LBE fusion proteins are useful as inhibitors of AGE/RAGE interaction, given that Neeper et al. teach that soluble RAGE is residues 1-344 of human RAGE, given that Peppel et al. teach that an extracellular receptor moiety-Fc fusion protein is a desirable inhibitor for the ligand-receptor interaction, given that Milne Edwards et al. teach that the claimed fusion proteins partners are desirable and given that all of the references concern treatment of inflammatory disorders, it

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would have been reasonable to predict that a fully functional fusion protein comprising the RAGE polypeptide disclosed Morser et al. and comprising the Fc fragment taught by Peppel et al. and comprising the other partners as taught by Milne Edwards et al. could be successfully produced and used for treatment of inflammation.

Moreover, regarding the potential fusion proteins partners of the claims (other than the RAGE-LBE polypeptides), inclusion of said partners is clearly the result of routine optimization of parameters (MPEP § 2144.05). It would have been customary for an artisan of ordinary skill to determine the optimal fusion protein partner for inclusion with RAGE-LBE given both Peppel et al.'s and Milne Edwards et al.'s explicit teachings of how to design such. At the time of the invention, all of the reagents were readily available and the technology existed to prepare fusion proteins as claimed and Milne Edwards et al. had demonstrated success in producing fusion proteins with no loss of function and being useful for therapeutic purposes. Thus one skilled in the art could have readily modified the RAGE-LBE containing fusion proteins of Morser et al. by optimizing them for therapeutic use as taught by Peppel et al. and Milne Edwards et al. Absent some demonstration of unexpected results from the claimed parameters, this optimization of proteins would have been obvious at the time of applicants' invention. Therefore, it would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to improve Morser et al.'s soluble RAGE fusion protein as disclosed by Peppel et al. and Milne Edwards et al. to yield predictable results. This is because the artisan has good reason to pursue the known options within

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his or her technical grasp. Such would amount to a substitution of known equivalent elements, one fusion proteins for another, to obtain predictable results.

It is noted that applicants have not traversed the previous rejection of claims 12-18, 20-31 and 42-44 under 35 U.S.C. 103(a) in the reply filed on 09 July 2009.

Therefore, the rejection of these claims stands for the reasons previously made of record.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory S. Emch whose telephone number is (571) 272-8149. The examiner can normally be reached 9:00 am - 5:30 pm EST (M-F).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey J. Stucker can be reached at (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/G.E./

Gregory S. Emch
Patent Examiner
Art Unit 1649
16 November 2009

/Daniel E. Kolker/
Primary Examiner, Art Unit 1649
November 19, 2009